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Clinical Review

Acne

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The cause of acne is still obscure, but genetic predisposition, sebaceous overactivity, overgrowth of bacterial flora and exposure to comedogenic substances are all significant factors.

Acne lesions occur mainly in sebaceous follicles, which are characterized by deep follicular canals and large sebaceous glands. The associated seborrhea is not due to a circulatory excess of androgens but may be caused by a local amplification of androgenic activity. This, in turn, may be due to large numbers of androgen receptors and a high concentration of enzymes such as 17β-hydroxysteroid dehydrogenase, within the sebaceous gland itself. Hyperkeratosis of the retention type in the pilary infrainfundibulum obstructs the outflow of sebum and keratin flakes. This favors the proliferation of Propionibacterium acnes which may initiate inflammation in microcomedos and lead to formation of pustules, papules or nodules.

Topical therapy with tretinoin, benzoyl peroxide and antibiotics such as clindamycin is widely used today. Oral tetracyclines and other chemotherapeutic agents remain necessary in severe cases.

ACNE VULGARIS is the most common disorder of the pilosebaceous system. Favoring areas where sebaceous glands are numerous, it usually affects the face and less frequently the back, and very often it is associated with increased oiliness of the skin. Acne is characterized clinically by the appearance of comedones, pustules, papules and nodules, and is easily diagnosed. Most cases run a protracted course with frequent relapses.

Acne usually begins at puberty and affects most teenagers to some degree. On average, it reaches peak severity in girls at 14 years and in boys at 16 years, and most cases improve by the late teens or early 20's. It may persist until the mid-30's and, often, greasy cosmetics aggravate the condition. In some women, acne does not develop until the late teens or early 20's, but in 3 percent of them it develops well before the onset of the other features of puberty.

The clinical course of acne is influenced largely by genetic factors. However, transient relapses before menstrual periods often occur; various exogenous factors of physical and chemical nature may aggravate acne, and masculinizing conditions can also precipitate the disease. Remissions of acne are common after exposure to the sun.

The treatment of acne, although not curative,

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is successful in controlling the disease in most patients. After resolution of the condition, seborrhea and scarring may persist.

Etiology[1]

Genetic factors. Heredity plays an important role in the development of acne, with a family history of acne being present in 70 percent of cases. Acne is almost sure to develop in those whose parents are or have been affected or in those whose twins have the disease.

Endocrine factors. Circulating androgens must be present if acne is to appear. It is well known that the disease does not occur in male castrates but often does so in women with masculinizing tumors. Acne may improve in pregnant women or with the use of the "maxi-pill" (a high-estrogen content oral contraceptive containing 100 μg of mestranol), but often deteriorates in the premenstrual week. Estrogen can suppress sebum formation, but progesterone has no definite effect.

Bacterial infection. Propionibacterium acnes is present in pilosebaceous follicles and may play a major role in the induction of acne pustules. Superinfection with Gram-negative organisms during antibiotic therapy can also complicate the disease.

Physical and chemical factors. A variety of cosmetics, drugs, other chemicals, mechanical factors and certain types of irradiation may be acnegenic.

Stress factors. Although stress has not been shown to cause acne, it can aggravate the condition, possibly by inducing neurotic excoriation.

Diet. Dietary factors have little importance in acne but, occasionally, the intake of certain foods may appear to be associated with a mild flare of the condition.

Weather and environment. Ultraviolet light is beneficial and acne tends to improve slightly in summer, although it can become much worse in hot, humid conditions found in the tropics.

Racial factors. These factors are of little importance although acne seems less common in Japanese people.

Anatomy and Physiology of the Pilosebaceous System

The pilosebaceous system consists of hair follicles and sebaceous glands. The follicles slant to the skin surface and contain hairs deeply rooted in subcutaneous tissue. The sebaceous glands are intradermal with short ducts opening into the upper part of the follicle. Above this level the pilary canal broadens out and is called the infundibulum.

Hair follicles. There are three types of hair follicles on the face.[2] Terminal follicles contain long, thick, stiff beard hairs which fill the pilary canal. The accompanying sebaceous glands are of normal intermediate size, and the infundibula are short and lined with epithelium that is well developed and keratinized and has a normal barrier function. Continuous desquamation of individual cells occurs to prevent obstruction of the follicular orifices.

Vellus follicles are small structures containing soft hairs which are short and thin. The sebaceous glands are small but active. The follicular pores are minute but their patency is maintained. They far outnumber sebaceous follicles and produce appreciable amounts of sebum.

Sebaceous follicles are limited to the face and upper trunk. They are characterized by deep, cavernous follicular canals, wispy hairs, and large sebaceous glands. The terminal fifth of the infundibulum, or acroinfundibulum, is lined with normal squamous epithelium. The internal four fifths, or infrainfundibulum, is lined with a glycogen-rich epithelium. Its granular layer is meager and its thin keratin layer lacks a normal laminated structure. It sloughs readily to form a loose, porous mass of horny detritus in the follicular canal, or sebaceous filament, which permits sebum to flow through it. The patency of the infundibulum is not easily maintained as it lacks rigid terminal hairs that act as wicks for the outward flow of sebum. It is not surprising that most acne lesions occur in sebaceous follicles.

Sebaceous glands. The function of sebaceous glands in humans is unknown. They are found predominantly in the "sniffing" areas.[3(p63)] They are densest on the scalp, forehead, cheeks and chin, less dense on the back and least dense on the extremities. Sebaceous glands are lobulated and divided into acini by septa. A peripheral pool of undifferentiated basal cells lines the acini.[4] Their lipid content is minimal. They may contain considerable amounts of 17β-hydroxysteroid dehydrogenase,[5] an enzyme possibly involved in androgen synthesis.[6] These cells are metabolically active and replace the steady loss of mature cells in the central pool. Mature cells are swollen with lipids and may contain 3β-hydroxysteroid dehy-

drogenase, an enzyme which is possibly involved in a detoxicating pathway for androgens. The cells eventually burst in the center of the acini, releasing lipids and traces of keratin. This process takes three weeks and the sebum reaches the skin surface a week later.[7(p21)] Sebum is a holocrine secretion that flows slowly from the gland into the hair follicle via one or more sebaceous ducts. In young people there is a good correlation between the size of sebaceous glands and secretory activity. Also, the diameter of each skin pore is roughly proportional to the size of the gland.

Pure sebum consists of 60 percent triglycerides, 20 percent wax esters, 10 percent squalene and 10 percent miscellaneous substances. Lipids elaborated by the epidermis contain mainly cholesterol, sterol esters and phospholipids, and make up only 3 percent of the skin surface lipid film on the face, but proportionately more on the limbs. Variable proportions of the triglycerides in sebum are broken down to fatty acids by lipolytic bacteria and yeasts in the sebaceous follicle. Free fatty acids found on the skin surface reflect intrafollicular bacterial activity.

Sebaceous glands have no nerve supply and are under hormonal control. Their activity is mediated by androgens from the testes, ovaries and adrenal glands. Androgens may be metabolized differently in sebaceous glands to enhance their effects. For example, serum-transport testosterone is converted by 5α-reductase in the skin to 5α-dihydrotestosterone, a more potent stimulator of sebaceous activity. This diffuses through the sebaceous cell membrane into the cytoplasm where it is thought to attach itself to a specific cytosol receptor protein which then transports it to the cell nucleus and retains it there.[8] Prolonged androgenic activity could result in production of messenger RNA causing cytoplasmic biosynthesis of sebum and more androgen receptor protein. In addition, in certain body sites the principal adrenal androgen dehydroepiandrosterone may be converted by 17β-hydroxysteroid dehydrogenase in the undifferentiated sebaceous cell pool to more potent stimulators of sebaceous activity such as dihydrotestosterone and 5α-androstane-3β-17β-diol.[9] Pituitary gonadotrophins may also stimulate sebaceous activity via androgen release from ovaries or testes. Thyroid stimulatory hormone and growth hormone probably act in a permissive way allowing androgens to stimulate sebaceous activity. A pituitary sebrotrophic hormone has been suspected but not proven to occur in humans, although a β-lipotrophin is a possibility.[3(pp152-155)] Estrogens have no effect in physiologic doses but in high doses reduce sebum production 50 percent to 70 percent by suppressing pituitary gonadotrophins. The "maxi-pill" may reduce sebum production by 20 percent to 40 percent. Progesterone has no appreciable effect on sebaceous activity. Adrenal corticosteroids and corticotrophins do not enlarge sebaceous glands.

The acroinfundibulum is colonized by Staphylococcus epidermidis and the lipophilic yeasts, Pityrosporon ovale and P. orbiculare. These are aerobic and have lipolytic activity, but are too superficially located to be of practical importance. Propionibacterium acnes, an anaerobic, Gram-positive diphtheroid colonizes the depths of the infundibulum. It produces lipases, proteases, lecithinase, hyaluronidase and neuraminidase and is itself comedogenic.

The Pathogenesis of Acne

Obstruction of the pilosebaceous canal. Acne is a disease of the sebaceous follicles, and probably originates in those containing sebaceous filaments. There may be an androgen-dependent, inherent defect in the rate of follicular keratinization in acne-prone patients which could lead to the retention-type hyperkeratosis seen in the infrainfundibulum in acne. Initially, the epithelium develops a definite granular layer and lipid accumulates in the epidermal cells. There is also a reduction in the number of keratinosomes (lamellar granules), lysosome-like organelles, which discharge their contents into the intercellular spaces, possibly dissolving the polysaccharide cement there.[10] There is an increased turnover of the follicular epithelium leading to a higher output of horny cells which stick together and do not slough away readily.[11] The follicular canal fills with solid horny detritus and a microcomedo forms which prevents the passage of sebum. The acroinfundibulum is not involved so the follicular orifice does not dilate and remains inconspicuous. This closed comedo gradually enlarges and may take five months to reach 2 mm in diameter and become clearly visible as a whitehead. Closed comedones are the "time-bombs" of acne because they obstruct follicular drainage and eventually rupture to cause inflammatory lesions.[7(p59)] Some gradually transform into open comedones or blackheads which protrude through and dilate the follicular orifice, relieving mechanical obstruction and losing the tendency to

rupture. They are chronic, stable lesions which accumulate keratin, lipid and exfoliated hairs. Their apical black color is due to melanin from the acroinfundibular epithelium.[12] When blackheads are present in excess, inflammatory lesions diminish.

Enlargement of sebaceous follicles. Enlarged sebaceous glands and seborrhea are features of adolescent acne, although serum androgen levels are normal. An end-organ hypersensitivity to androgens is postulated, possibly due to overproduction of testosterone,[13] increased numbers of androgen receptors[14] and increased amounts of 17β-hydroxysteroid dehydrogenase. Higher levels of pituitary sebotrophic hormone, if it exists in humans, may also play a role. The net result is marked sebaceous overactivity which is generally proportionate in severity to the acne.

Changes in skin lipid composition. Triglycerides, wax esters and squalene are increased in acne. Total free fatty acids may be decreased in males but not in females and sebaleic acid is increased in both.[15] Squalene, certain free fatty acids and even wax esters are comedogenic in humans and may lead to early changes in the infrainfundibular epithelium from primary irritation.

Increased bacterial flora. Propionibacterium acnes thrives in comedones and, in addition to splitting triglycerides into free fatty acids, can release other inflammatory mediators like proteases and hyaluronidase. The organism also possesses antigenic properties and can cause immediate and cell-mediated immune reactions which may increase its inflammatory potential. Recent work has shown that at the levels actually present in comedones, free fatty acids are not inflammatory agents in acne, as previously thought.[16,17] It seems likely that important causes of inflammation in acne are the *P. acnes* organisms themselves, as well as insoluble substances such as keratin fragments and hair.

The Evolution of Acne Lesions

Comedo. The dangerous lesions in acne patients are the closed comedones, often at the microcomedo stage which may be invisible. The earliest inflammatory lesion is probably caused by the accumulation of toxic material from bacterial activity. Leukotactic substances diffuse out through the intact follicles and attract neutrophils. These cells cause an intrafollicular abscess which later liquefies and may escape into the dermis, forming a perifollicular abscess.

Pustule (transient papulopustule).[7(pp140-142)] Superficial follicular "blowouts" lead to small elevated lesions which are short-lived. Deeper follicular ruptures cause deep-seated, more chronic lesions. The lesions liquefy often causing the overlying roof to rupture and the comedonal remnants and pus to be discharged onto the skin surface. The breaks in the follicular epithelium are later repaired. This leads to reversion to a sebaceous follicle, or to the formation of secondary comedones, which either become cystic or connect with neighboring lesions to become polyporous. Minimal scarring results.

Papule (nontransient type). More severe inflammation may lead to total collapse of the comedo and destruction of most of the follicular lining. Surface rupture is exceptional and usually lipids, horny detritus and hairs escape into the dermis and form foreign-body granulomas, which may take weeks or months to resolve. Obvious scarring is the final result.

Nodule. Here, there is total disintegration of one or more comedones with the formation of large abscesses involving neighboring follicles. The lesions are serous, hemorrhagic and dissect down to the subcutaneous fat, forming necrotic lesions 1 to 3 cm in diameter. Comedonal remnants and hairs in the tissues lead to foreign-body reactions. Healing takes months and gross scarring results.

Draining sinus. This results from a nodular lesion in which remnants of follicular epithelium survive and form interconnecting tunnels, lined with hyperplastic epithelium. Large, tender lesions are formed which periodically drain and then crust over. Acute and foreign-body type inflammatory changes occur. Again, scarring is inevitable.

Types of Acne Vulgaris

Comedonal acne. This is the mildest type of acne vulgaris, in which whiteheads and blackheads predominate, with minimal inflammatory lesions.

Papulopustular acne. This is a mixture of relatively few comedones with many inflammatory lesions, both superficial and deep.

Acne conglobata. This is the most severe and chronic form of acne in which inflamed nodular and draining lesions predominate and few primary comedones are seen, although secondary come-

dones are often formed. It occurs mainly in white males with severe seborrhea, is worst on the trunk and even involves buttocks and thighs.

Classification of the Acnes[7(p223)]

True acne. Varieties of acne vulgaris include premenstrual acne, menopausal acne, neonatal acne, pyoderma faciale, acne fulminans, acne tropicalis, masculinizing syndromes, acne mechanica and Gram-negative folliculitis. Varieties of acne venenata due to external agents include acne cosmetica, pomade acne, chloracne, oil and tar acne, detergent acne and acne aestivalis. Varieties of comedonal acne due to physical agents include comedones in aging skin and comedones from ionizing radiation.

Acneform eruptions. These are follicular reactions starting with inflammatory changes. Comedones are rare. Causes include iodides, bromides, isoniazid, corticosteroids and corticotrophin, diphenylhydantoin and phenobarbitone.

Acne neonatorum may affect neonates for a short while due to maternal or fetal androgens. Infantile acne occurs later, lasts longer, and may be due to a transient increase in gonadal testosterone.

Pyoderma faciale or explosive postadolescent facial acne of females affects women in their 20's and 30's who have a history of recent major, emotional trauma. It resembles acne conglobata on the face with inflamed lesions which are tender and purplish. It is heralded by severe seborrhea.

Acne fulminans, a rapidly progressing severe and widespread acne with painful ulcerative lesions filled with gelatinous material, occurs most frequently on the trunk. Comedones are rare. There are associated findings such as fever, leucocytosis, a raised sedimentation rate, anemia and polyarthritis.

Gram-negative folliculitis sometimes occurs during long-term treatment of acne with antibiotics. Resistant Gram-negative bacilli colonize the anterior nares and spread out to cause pustules (Enterobacter and Klebsiella) or nodules (Proteus).

Acne cosmetica affects women 20 to 50 years old, usually on the chin and checks. It is caused by foundation creams, night creams, moisturizers, sunscreens and other cosmetics that contain comedogenic substances.

Treatment of Acne Vulgaris

There is no definite cure for acne. Therapy is aimed at keeping the condition under reasonable control and trying to prevent the severe flares that lead to scarring. Therefore, treatment is often necessary for prolonged periods until, eventually, spontaneous resolution occurs.

General Scheme of Treatment

Comedonal acne. Topical exfoliants such as benzoyl peroxide, retinoic acid and salicylic acid are sufficient. Comedo extraction is helpful cosmetically.

Papulopustular acne. Topical exfoliants and oral and topical antibiotics will control most cases.

Acne conglobata. Exfoliants, oral and topical antibiotics and dapsone may help. Sometimes systemic corticosteroids may be required as well. Carefully controlled radiation therapy can benefit selected cases, but must be used with great caution. Despite the current controversy about the risk of thyroid neoplasms, the evidence supporting this possibility seems insufficient to exclude every patient from this method of treatment.[18]

Specific Forms of Treatment

Exfoliants. These may either have comedolytic effects which retard the formation of new comedones as well as quickening the shrinkage of these already formed or have counterirritant effects which increase blood supply and shorten healing time. Retinoic acid or tretinoin, available as a gel, cream or lotion, is an effective comedolytic agent.[19] It interferes with comedo formation by reducing corneocyte adhesion. It also intensifies follicular epithelial proliferation and turnover, thereby assisting in loosening and expelling the comedones. It thins follicular epithelium and renders it more permeable to toxins that may leak through and cause lesions to rupture externally, and also stimulates increased blood flow. It may cause stinging, burning, redness and peeling, and treatment must be started with caution. It also causes a transient outcrop of pustules after three to four weeks in a third of cases. Side-effects often induce patients to abandon therapy but, generally, these improve within two months in those who persevere. Long-term treatment is usually needed to maintain a beneficial effect. However, retinoic acid increases skin susceptibility to sunlight, and its possible influence on the incidence of sun-induced skin cancer is currently under investigation. It should, therefore, be used with great caution in patients exposed to excessive

sun, wind or cold, as well as in those with a genetic predisposition towards undue sun-damage and skin cancer.

Benzoyl peroxide in a stable gel form, preferably alcohol-based, is a useful exfoliant that is also bacteriostatic, which enhances its value. It is available in 5 percent and 10 percent concentrations. It, too, has to be used with caution until the patient can tolerate it. It works well on its own, but if comedones predominate may be used in conjunction with retinoic acid—one being used in the morning and the other at night. Miscellaneous exfoliants are available and salicylic acid 5 percent or 10 percent in 85 percent ethanol and 15 percent propylene glycol is also effective. Elemental sulfur still has its supporters though others condemn it when used alone. Abrasive soaps and sponges are not comedolytic but may help scour away papulopustular lesions. Ultraviolet light increases blood supply and helps resolve inflammatory lesions. Cryotherapy also helps to clear inflamed lesions and may be useful in the treatment of shallow scars.

Antibiotics and chemotherapeutic agents. To eradicate Propionibacterium acnes effectively these agents have to achieve adequate concentrations in the pilosebaceous follicles. Orally given tetracyclines have this ability and long-term, low-dosage tetracyclines have been the mainstay of acne therapy for years. Side-effects are mild and include mild gastrointestinal upsets and candidiasis. These drugs are contraindicated in treating children below eight years, in pregnant women and in patients with renal disease. They lead to the development of resistant Gram-negative commensals which become R-factor carriers. They do not produce serious consequences but may lead to Gram-negative folliculitis. Another useful drug for treating acne is erythromycin. Clindamycin is extremely effective but occasionally causes pseudomembranous colitis. It is active topically and local application twice per day is sufficient.[20] A suitable lotion consists of 600 mg of clindamycin dissolved in 48 ml of 70 percent isopropyl alcohol, 6 ml of water and 6 ml of propylene glycol. Clindamycin is currently under trial to establish its safety as a topical agent. Safe alternatives include erythromycin or tetracycline in a hydroalcoholic vehicle.

Cotrimoxazole (combination of trimethoprim and sulfamethoxazole) can be extremely useful in patients who have become refractory to tetracycline and erythromycin. It may be given in small dosages of 1 to 2 tablets each day for up to three months. In severe cases, dapsone in a dosage of 100 to 150 mg per day may be useful if given with tetracycline for two to three months. Patients given long-term dapsone or cotrimoxazole should have periodic checks of the peripheral white blood cells because both have been reported to cause neutropenia. Neither of these drugs is listed by the FDA as being indicated for acne, so caution in their use is appropriate. Orally given zinc may be effective in the treatment of acne,[21] but larger trials are required to confirm this, as its value is disputed.[22]

Reduction of sebum output. One course of x-ray therapy limited to a total of 1,000 to 1,200 rads can produce a temporary decrease in sebum production of up to 80 percent. It may still be indicated in occasional severe and refractory cases but its possible carcinogenic effects must be borne in mind and shielding of the neck is essential. To produce a substantial decrease in sebum output, estrogens usually have to be given in high doses and unacceptable side-effects result. The "maxi-pill" may be beneficial in mild cases. Therefore, the search for a suitable antiandrogen which is effective topically continues.

Miscellaneous treatments. Diets, vitamins and psychotherapy have no proved value in the treatment of acne. However, oral 13-cis-retinoic acid, still an experimental drug, may prove to be helpful in treating severe forms of acne.[23] Many of the traditional topical agents are useless and some are harmful. Many oily substances in cosmetics are comedogenic and must be avoided. Topical corticosteroids are contraindicated, although intralesional steroid injections may be helpful, especially for nodulocystic lesions. Sometimes, treatment with systemic corticosteroids is necessary for short periods in fulminating cases of acne.

Acne surgery. Procedures for abscess drainage should be kept to a minimum in scope and size as it is easy to cause unsightly scars. Intralesional steroids, chemosurgery, cryosurgery, plastic surgery and, occasionally, dermabrasion have their place in experienced hands in the treatment of acne scarring. It is better to delay surgical procedures until the acne process is completely controlled. Acne scars often improve considerably with time and may take at least a year to reach their final size and shape. Older scars are less likely to respond to intralesional steroids, and

plastic surgical treatment of individual lesions may be of considerable benefit.

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Anticipating Arrhythmias

ATTENTION TO DETAIL is all important in cardiac arrhythmias. Find out when your patient has arrhythmias. Sometimes arrhythmias cluster in certain periods of the day. And if that is the case, then you want to tailor your therapy so that the patient gets the maximum therapy before he is apt to have these arrhythmias. If in fact the arrhythmias cluster in the morning or evening, let's say, then organize your therapy around that—and give the patient a larger dose of antiarrhythmic medication an hour or so before the arrhythmias are expected.

—G. CHARLES OLIVER, MD, *St. Louis*

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